IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Scott Miller — Examiner: KUMAR, Shailendra

Serial No.: 09/776,936 — Group Art Unit: 1621

Filed: 12/22/98

Title: INHIBITION OF RAF KINASE USING SYMMETRICAL AND UNSYMMETRICAL SUBSTITUTED DIPHENYL UREAS

APPEAL BRIEF

Mail Stop: **AF**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Notice of Appeal filed on May 3, 2012, please consider the following.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

REAL PARTY IN INTEREST

The real party in interest is Bayer Healthcare LLC.

RELATED APPEALS AND INTERFERENCES

There are no known related appeals or interferences.

SUMMARY OF CLAIMED SUBJECT MATTER

Appellants' invention in independent claim 36 is directed to compounds according to formula I in crystalline form or in a solvated form (see, for example, page 16, lines 12-30 and the examples), which are aryl urea compounds (see, for example, on page 2, line 22 to page 4, line 12, and page 5, line 1 to page 7, line 10, and also the specific compounds in the tables on pages 62 to 74), which have a pKa greater than 10 (see, for example, in

original claim 2 on page 79, line 4 and on page 2, line 22 to page 4, line 12, and page 5, line 1 to page 7, line 10).

ARGUMENT

The only issue is the rejection of solvates as allegedly lacking written description.

The final Office Action mailed February 3, 2012 (final Office Action hereinafter), alleges

> Not only applicants are not in possession of the solvate, from the instant specification, it appears that applicants have no intention of claiming solvate because they have not mentioned the word solvate not even once and no solvate has been made in the examples.

However, "The test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language." See *Chiron Corp. v. Genentech Inc.*, 70 USPQ2d 1321 (CAFC 2004).

Whether applicants had the intention of claiming solvates when the application was originally filed is irrelevant to the inquiry whether the application does or does not provide written description to the presently claimed invention, which includes solvates.

As such, the absence of literal support in the specification for the term solvate or the lack of an original claim directed to a solvate is not determinative of whether applicants adequately described the claimed invention.

It is well known and not at dispute that a solvate forms by the aggregation or co-crystallization of a compound molecule and one or more guest molecules, e.g., solvents of crystallization. See, *Braga et al.*, Making crystals from crystals: a green route to crystal engineering and polymorphism, Chem. Commun., 2005, 3635-3645, page 3636, first column (*Braga* having been cited by the final Office Action).

The specification of the present application clearly teaches the concept of solvates by disclosing specific embodiments of combinations of compounds of the claims with solvents. The application provides numerous examples where a solvent was brought together with a compound of the application leading to the formation of a solid material.

See the General Methods of Urea Formation from page 51 to page 61, followed by the tables of compounds prepared from page 62 to 74. In the tables, there is a column providing the "Solvent System" and another column providing the "Synth. Method." For example, compound 1, has been prepared by synthetic method B1d, which method is described on pages 52-53, which discloses taking the reaction product prepared in said example's first part, i.e., a resulting precipitate, and washing with Et_2O to give the title compound as a white solid. See, also, for example, entry 9 in table 1 on page 62 of the specification, which is synthesized using method B5. This method describes the desired compound being formed in solution involving the interaction between a compound and a solvent. Most, if not all, of the examples given in the specification require the compounds to be synthesized in solution through the combination of compounds with solvents. As such, the specification is replete with examples disclosing the concept of solvates. Thus, the disclosure demonstrates that the applicants were in possession of the claimed subject matter at the time of filing.

Also note that the descriptions of the methods clearly and explicitly disclosing the formation of crystals of compounds of the application in the presence of solvates. Especially see section C. Urea Interconversions and Misc. Reactions, starting on page 59, therein more specifically subsection C4. General Method for Deprotection of tert-Butyl Carbonate-Containing Ureas, on page 61 teaching that the resulting white foam of the reaction was triturated (Et_2O/hexane), then recrystallized (Et_2O) to give the desired product.

Moreover, the disclosure on page 16, lines 8 to 13 provides a disclosure of transdermally administering a compound of Formula I in a suitable volatile solvent, with suitable solvents being disclosed on the same page, lines 19-26.

As such, the disclosure explicitly teaches the formation of solids, including crystals, of compounds of the application in the presence of solvents, and further teaches the combination of compounds of the application with solvents, for, e.g., transdermal systems.

While the term "solvate" does not explicitly appear in the disclosure, one of ordinary skill upon reading the disclosure and seeing, especially, the formation of various solids and crystals of compounds of the application in the presence of solvents, would have understood that the inventors had possession of solvates of the claimed invention

even absent an explicit recitation of said term. Such is especially the case where one or ordinary skill in the art knows that solvate formation is "very common." See, e.g., *Braga et al.*, supra, page 3640, second column, in the paragraph spanning the first and second columns. See also *West*, Solid State Chemistry and Its Applications, Wiley & Sons, 1989, Chapter 10, page 358, starting said chapter with "Solid solutions are very common in crystalline materials" (*West* having been cited by the final Office Action).

The non-final Office Action mailed on September 13, 2011 (non-final Office Action), took a different approach than the final Office Action in rejecting the claims for an alleged lack of written description. Said non-final Office Action alleges that the compounds of formula I being in solvate form is a "critical element" of the claims.

The USPTO Guidelines for Written Description, relied upon by the non-final Office Action, define critical elements as follows: "The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art." (Emphasis added.) Converting base urea compounds to solvate form is conventional in the art and well known to one of ordinary skill in the art.

See the previous Appeal Brief filed on June 20, 2011, in this application in support, where the issue was whether the solvates at issue herein are enabled. The Examiner reconsidered said rejection after the filing of the previous Appeal Brief. As established in said Appeal Brief, the art is abundant regarding solvates of pharmaceutical compounds, and includes guidance on how to produce them, characterize them, etc.

A quick search of the art further reveals that even back as far as the early 1980's and 1990's solvates of urea compounds were known by those of ordinary skill in the art. See, for example, US Pat. 5,786,448, US Pat. 5,905,080, and US Pat. 4,379,786, all of which teach solvates of urea compounds. US Pat. 4,379,786, having a filing year of 1981 and having been filed by an independent party from applicants, for example, on column 4, lines 7-13, teaches:

> The preferred salt forms of I are additionally capable of forming hydrates and solvates with H_2O and certain organic solvents, respectively. Also, I and its salt forms may exist in several tautomeric forms. It is naturally intended that the various hydrates, solvates, and tautomeric forms of I be included within the scope of this invention.

The final Office Action commented on applicant's submission of the above cited US patents establishing the state of the prior art by stating that applicants "cite some old patents" and that "none of the patents that applicants are citing are claiming hydrates of solvates."

The fact that the cited art is "old," strongly supports applicants' position that the solvates of the type of compounds in the present claims are known to exist in the art for a long time. And that no claims in said cited art is directed to solvates is irrelevant. The teaching of solvates of urea compounds is present in the cited references irrespective of whether or not an issued claim has been directed to solvates.

The above cited language from US '448 clearly shows that even as far back as 1981, one skilled in the art would "naturally" include solvates when presented with a urea compound. The critical elements of the rejected claims are the compounds of formula I, which are well defined in the specification. That the compounds of formula I are in a solvate form is not a critical element, as one of ordinary skill in the art expects that the compounds of the present claims could form solvates. In this regard, again see the previously filed Appeal Brief, as a result of which, the allegations of a lack of enablement of solvates have been withdrawn.

The subject matter of the claims must be described so as to reasonable convey to one skilled in the art that the inventors had possession of the claimed invention at the time of filing. Applicant's respectfully submit that the specification which describes the compounds of formula I and provides examples of said compounds in combination with various solvents, and teaches the formation of various solid forms of the compounds, e.g., crystals, precipitates, etc., does reasonable convey to one skilled in the art that the inventors had possession of the solvate forms of the compounds of formula I in view of the state of the art. As discussed above, one skilled in the art would know that as far back as 1981, "It is naturally intended that the various hydrates, solvates, and tautomeric forms of I be included within the scope of this invention," US '786, supra, for urea compounds.

Also relevant to the analysis is *Capon v. Eshhar,* 76 USPQ2d 1078 *(Fed. Cir. 2005)* where a specification gave no examples of the involved genus, i.e., of nucleotide or amino acid sequences, but merely relied on prior art knowledge, and yet was held to provide an adequate written description. Similarly to the situation in *Capon*, one of ordinary skill in the art can make the claimed solvates and the art is abundant on solvate

formation, including on the type of compounds at issue. These factors in view of *Capon* weigh heavily in finding adequate written description in the present case. "When the prior art includes the … information, precedent does not set a *per se* rule that the information must be determined afresh." *Id at 1358*.

For all the foregoing, reversal of the rejection is respectfully and courteously requested.

Respectfully submitted,

/Csaba Henter/

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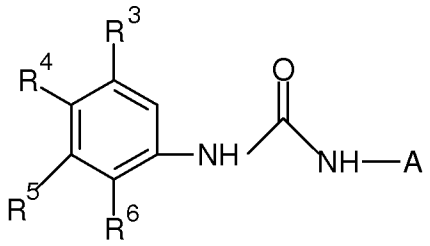
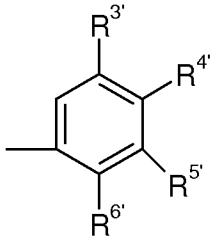
CLAIMS APPENDIX

36. A compound of formula I, which is in crystalline form or in a solvated form:



I

wherein A is



,

R^3, R^4, R^5 and R^6 are each, independently, H, halogen, NO_2,

C_{1-10}- alkyl, optionally substituted by halogen up to perhaloalkyl,

C_{1-10}-alkoxy, optionally substituted by halogen up to perhaloalkoxy,

C_{1-10}- alkanoyl, optionally substituted by halogen up to perhaloalkanoyl,

C_{6-12} aryl, optionally substituted by C_{1-10} alkyl or C_{1-10} alkoxy, or

C_{5-12} hetaryl, optionally substituted by C_{1-10} alkyl or C_{1-10} alkoxy,

and either

one of R^3, R^4, and R^5 is –M-L^1; or

two adjacent of R^3, R^4, R^5 and R^6 together are an aryl or hetaryl ring with 5-12 atoms, optionally substituted by C_{1-10}-alkyl, , halo-substituted C_{1-10}-alkyl up to perhaloalkyl, C_{1-10}-alkoxy, halo-substituted C_{1-10}-alkoxy up to perhaloalkoxy, C_{3-10}-cycloalkyl, C_{2-10}-alkenyl, C_{1-10}-alkanoyl, C_{6-12}-aryl, C_{5-12}-hetaryl; C_{6-12}-aralkyl, C_{6-12}-alkaryl, halogen; NR^1R^1; -NO_2; -CF_3; -$COOR^1$; -$NHCOR^1$; -CN; -$CONR^1R^1$; -SO_2R^2; -SOR^2; -SR^2;

in which

R^1 is H or C_{1-10}-alkyl, optionally substituted by halogen up to perhaloalkyl and

R^2 is C_{1-10}-alkyl, optionally substituted by halogen, up to perhaloalkyl,

$R^{3'}$, $R^{4'}$, $R^{5'}$ and $R^{6'}$ are independently H, halogen,

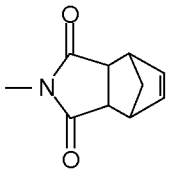
C_1 - C_{10} alkyl, optionally substituted by halogen up to perhaloalkyl,

C_1 –C_{10} alkoxy optionally substituted by halogen up to perhaloalkoxy or two adjacent of $R^{3'}$, $R^{4'}$, $R^{5'}$ and $R^{6'}$, together with the base phenyl, form a naphthyl group, optionally substituted by halogen up to perhalo, C_{1-10} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkyl, C_{2-10} alkenyl, C_{1-10} alkanoyl, C_{6-12} aryl, C_{5-12} hetaryl or C_{6-12} aralkyl;

M is $–CH_2$-, -S-, $-N(CH_3)$-, -NHC(O)- $-CH_2$-S-, -S-CH_2-, -C(O)-, or –O-; and

L^1 is phenyl, substituted by C_{1-10}-alkoxy, OH, $-SCH_3$, or by

pyridyl, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, OH, $-SCH_3$, or NO_2,



naphthyl, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, OH, $-SCH_3$ or NO_2,

pyridone, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, OH, $-SCH_3$ or NO_2,

pyrazine, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, OH, $-SCH_3$ or NO_2,

pyrimidine, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, OH, $-SCH_3$ or NO_2,

benzodioxane, optionally substituted by C_{1-10}-alkyl, C_{1-10}-alkoxy, halogen, OH, $-SCH_3$ or NO_2,

benzopyridine, optionally substituted by C_{1-10}-alkyl, one C_{1-10}-alkoxy, halogen, -OH, $-SCH_3$ or NO_2 ,

or

benzothiazole, optionally substituted by, C_{1-10} alkyl C_{1-10} alkoxy, halogen, OH, $-SCH_3$ or NO_2,

and wherein the compound of formula I has a pKa greater than 10,

or a pharmaceutically acceptable salt thereof.

39. A method for treating cancer comprising administering a compound according to claim 36 to a subject in need thereof in an effective amount, which compound is in solvated form.